

# Human Fascioliasis (Liver Fluke Disease) in Hawai'i: Case Report and Review of Human Fascioliasis Acquired in the United States

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## Abstract

*Fascioliasis is a foodborne zoonotic infection caused by the trematode liver flukes: Fasciola hepatica and Fasciola gigantica (F. gigantica). Infections may cause acute and chronic hepatobiliary tract diseases in herbivore animals and humans. Fascioliasis is present worldwide, particularly in regions where sheep and cattle are raised. The global burden of human fascioliasis is estimated to be 2.7 million. Human infections are rare in the United States, and most infections were acquired abroad. In the 1950s, several human cases of F. gigantica infection were reported from Hawai'i, but no subsequent cases have been reported until the case described here.*

*This case report describes a man from Hawai'i Island who ate raw wild watercress, and 22 days later, developed acute phase fascioliasis with fever, acute hepatitis, peripheral eosinophilia, and hypodense lesions seen on liver diagnostic imaging. Immunodiagnostic tests were positive for Fasciola species. Based on earlier reports from Hawai'i, F. gigantica infection was likely. Clinical abnormalities resolved after treatment with triclabendazole. Physicians should consider fascioliasis in immigrants and travelers from endemic areas with acute hepatitis and eosinophilia after eating raw wild watercress or chronic hepatobiliary disease. Hepatobiliary imaging and serological testing are useful for diagnosis. Oral triclabendazole is the preferred treatment. Animal fascioliasis appears to be spreading in the United States, and the popularly perceived health benefits of eating raw wild watercress and other aquatic plants may lead to more human infections. The rarity of human infections in Hawai'i suggests that it is safe to eat commercially grown watercress cultivated in Hawai'i.*

## Keywords

Fascioliasis, Fasciola gigantica, Liver disease, Hawai'i, United States

## Abbreviations and Acronyms

CDC = Centers for Disease Control and Prevention

EIA = enzyme immunoassay

ELISA = enzyme-linked immunosorbent assay

ES = excretory-secretory

FAST = Falcon assay screening test

FDA = US Food and Drug Administration

RV = reference value

## Introduction

Fascioliasis is a foodborne zoonosis of animal herbivores caused by the parasitic trematodes (liver flukes), *Fasciola hepatica* (*F. hepatica*), and less commonly, *Fasciola gigantica* (*F. gigantica*).<sup>1</sup> Animal fascioliasis occurs on all continents except Antarctica. In the mid-1990s, human fascioliasis emerged in many countries worldwide, predominately in populations living in cattle and sheep-rearing regions with limited resources.<sup>2</sup> The estimated

global burden of human infection is 2.7 million.<sup>3</sup> The parasitic life cycle is complex.<sup>4</sup> Briefly, animal herbivores, typically domesticated cattle and sheep are the primary hosts, aquatic snails are the intermediate hosts, and freshwater aquatic plants are the means of transmission. Humans may become incidental hosts after eating raw aquatic plants (eg, watercress). Human fascioliasis is rarely reported in the United States, and most patients were immigrants or American travelers returning from endemic regions.<sup>5</sup> Hawai'i is considered an endemic area based on livestock studies and human cases reported in the 1950s.<sup>6</sup> However, no Hawai'i human cases have been reported subsequently. Informal inquiries of local Hawai'i infectious diseases and gastroenterology specialists found no cases diagnosed in the past 45 years. This case report describes a patient who developed acute phase hepatic fascioliasis acquired in 2008 after eating raw wild watercress on Hawai'i Island. Further, this report examines documented cases of human fascioliasis acquired in the United States.

## Case Report

A previously healthy 58-year-old man living in a rural area of Hawai'i developed chills and fevers approximately 101.5°F, followed by progressive fatigue, weight loss, diffuse pruritus, and moderate, intermittent pain in the right upper abdomen and right anterior lower chest. His past medical history was unremarkable. He was born and raised in the northern part of the United States and had not traveled abroad in 30 years. His initial physical examination was remarkable for a slightly tender liver felt 3 cm below the right costal margin and slight dermatographism. Laboratory studies revealed a leukocytosis of 12,600 cells/mm<sup>3</sup> with 33% eosinophils (absolute eosinophil count 4,158 cells/mm<sup>3</sup>). The combination of liver tenderness and eosinophilia in a patient on Hawai'i Island led an infectious disease consultant to suspect acute hepatic fascioliasis. Further history revealed that 2 weeks before the onset of symptoms, the patient had eaten a half-cup of raw wild watercress collected from a pond adjacent to a cattle pasture. Blood levels of liver-associated enzymes were elevated, with an alkaline phosphatase of 324 IU/L (reference value [RV]: 33–130), alanine aminotransferase 91 IU/L (0–40), and aspartate aminotransferase 43 IU/L (0–37). The serum bilirubin level was 0.7 mg/dL (RV: 0.2–1.5). Ultrasonography revealed multiple hypoechogenic areas in the liver, and a computed tomography scan showed multiple hypodense areas in the liver (Figure 1). *Fasciola* serologic testing by a commercial laboratory (Parasitic Disease Consultants, Georgia) using enzyme-linked immunosorbent

assay (ELISA) to crude *F. hepatica* worm extract was initially borderline positive with a titer of 1:32 (reference range: negative <1:32; positive >1:32). Six weeks later, the titer rose to 1:64, and the sample was also positive for antibodies against *Fasciola hepatica* excretory-secretory (ES) antigens by Falcon assay screening test ELISA testing done at the Centers for Disease Control and Prevention (CDC) reference Laboratory of Parasitic Immunology, San Juan, Puerto Rico. Pending availability of triclabendazole, an investigational drug, he was treated with 500 mg of nitazoxanide orally twice daily for 7 days without clinical improvement. A second nitazoxanide treatment also failed. The hospital's Institutional Review Board approved a US Food and Drug Administration (FDA) Investigational New Drug program. With the patient's consent, he was treated with 10 mg/kg of triclabendazole once by mouth with a meal. Following treatment, his symptoms resolved, and the blood eosinophil counts and liver-associated enzyme tests became normal 10 weeks later. *Fasciola* antibody levels gradually decreased and were normal 9 months after treatment. Eight stool specimens obtained before and after treatment were negative for ova and parasites. Although no adult parasites were recovered from this patient, the epidemiologic, clinical, and serological findings were strong evidence for acute hepatic phase fascioliasis. Based on earlier studies in Hawai'i, *F. gigantica* was probably the culprit species in this patient.<sup>6</sup>

## Discussion

### Fasciola Life Cycle and Epidemiology

The complex *Fasciola* life cycle is similar in both animal and human hosts. Adult *Fasciola* flukes dwell in the principal host's hepatobiliary system and produce eggs passed in the feces into freshwater environments (Figure 2). The eggs hatch into miracidia (immature larvae) that infect specific aquatic snail

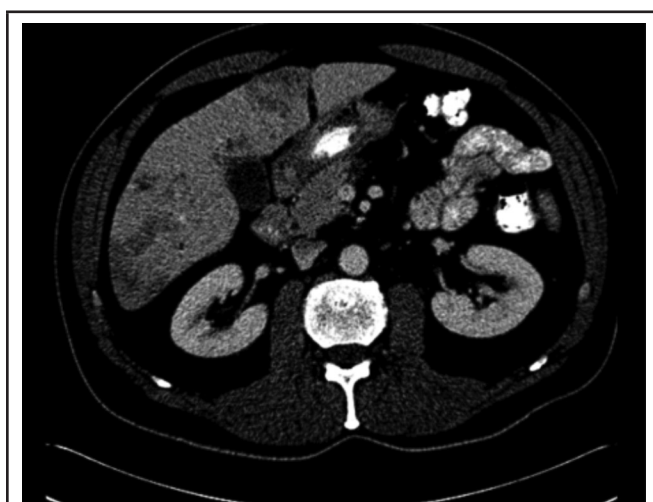


Figure 1. Contrast-Enhanced Computed Tomography of the Abdomen Showing Multiple Hypodense Areas in the Liver.

intermediate hosts, releasing cercariae that attach to aquatic plants as infectious metacercariae. After the host ingests the plants, the metacercariae excyst, become motile juveniles, which penetrate the host's intestines, enter the peritoneum, and invade the liver. In this acute phase of infection, the migrating juveniles move through the liver for several weeks, causing acute hepatitis and leaving visible tracks of destruction. Some juvenile flukes may appear in various ectopic sites, such as the skin and respiratory tract. In the chronic phase of infection, the larvae enter the host's hepatobiliary system, where they mature into adult egg-producing flukes to complete the life cycle. *F. hepatica* adult flukes are approximately 30 mm long, and *F. gigantica* adults are approximately 75 mm long (Figure 3). Adult flukes live in the hepatobiliary system for about 10 years. They might cause chronic or relapsing hepatobiliary tract-related diseases. In low-resource countries with poor sanitation, humans are infected by eating various freshwater aquatic plants grown

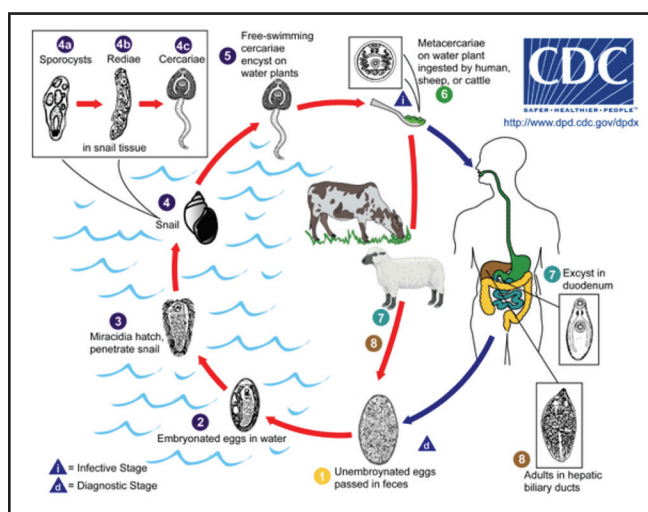


Figure 2. *Fasciola Hepatica* Life Cycle. Immature eggs are discharged in the biliary ducts and in the stool (1). Eggs become embryonated in water (2), eggs release miracidia (3), which invade a suitable snail intermediate host (4), including the genera *Galba*, *Fossaria*, and *Pseudosuccinea*. In the snail, the parasites undergo several developmental stages [sporocysts (4a), rediae (4b), and cercariae (4c)]. The cercariae are released from the snail (5) and encyst as metacercariae on aquatic vegetation or other surfaces. Mammals acquire the infection by eating vegetation containing metacercariae. Humans can become infected by ingesting metacercariae-containing freshwater plants, especially watercress (6). After ingestion, the metacercariae excyst in the duodenum (7) and migrate through the intestinal wall, the peritoneal cavity, and the liver parenchyma into the biliary ducts, where they develop into adults (8). In humans, maturation from metacercariae into adult flukes takes approximately 3 to 4 months. The adult flukes (*Fasciola hepatica*: up to 30 mm by 13 mm; *Fasciola gigantica*: up to 75 mm) reside in the large biliary ducts of the mammalian host. *Fasciola hepatica* infects various animal species, mostly herbivores. Source: <https://www.cdc.gov/parasites/fasciola/biology.html>

in wetlands adjacent to infected animal grazing areas or areas irrigated with contaminated water.<sup>7</sup> Infection can also occur after drinking contaminated water or ingesting food washed with the water. The means of disease transmission varies with local geographic agricultural and nutrition practices. In poor, hyperendemic regions, human feces may contribute to the spread of infection.<sup>7</sup> *F. hepatica* is found mainly in temperate regions and is responsible for most human infections. Human infections occur predominantly in the Andean Highlands of Latin America (Bolivia, Ecuador, Peru), North Africa, the Middle East (Egypt, Iran), East Asia (China), Iran, and to a lesser extent, Western Europe (Portugal, France, and Spain), and several Caribbean islands including Puerto Rico.<sup>2</sup> *F. gigantica* is closely related to *F. hepatica* and is found in tropical and subtropical regions of Africa, Asia, the Western Pacific, and Hawai'i. However, in Asia, the distribution of *F. hepatica* and *F. gigantica* overlap, making it difficult to identify the infective species unless adult flukes are recovered.<sup>2</sup>

### Clinical Features of Human Fascioliasis

The manifestations of human fascioliasis depend on the phase of the infection.<sup>1</sup> Many infections are asymptomatic, but infections may cause acute hepatitis or chronic relapsing hepatobiliary disease.<sup>8,9</sup> The clinical features of *F. hepatica* and *F. gigantica* infections are similar.<sup>10,11</sup> The acute liver phase is due to immature parasites migrating through the liver. Frequent complaints are right upper quadrant abdominal and epigastric pain, fatigue, and fever; other symptoms might include cough, pruritus, urticaria, and dermatographia. Less commonly, larval flukes may migrate to ectopic sites in the skin, respiratory system, pancreas, genitourinary tract, eyes, or brain. Laboratory studies during the acute phase usually show elevated liver-associated enzymes and intense blood eosinophilia. The chronic phase

of human fascioliasis begins several months later and may persist for years. Chronic fascioliasis is mainly asymptomatic, but ongoing hepatobiliary inflammation may manifest as liver fibrosis, cirrhosis, intermittent abdominal pain, biliary obstruction, cholangitis, and liver abscess, or pancreatitis. Eosinophilia is less common than during the acute stage, and eggs appear only intermittently in the feces. Chronic fascioliasis is usually unsuspected until adult flukes are discovered accidentally during surgery or endoscopy. Human infection with 2 other liver flukes, *Clonorchis sinensis* (Chinese or oriental liver fluke) and *Opisthorchis viverrini* (Southeast Asian liver fluke), can induce liver cancer and cholangiocarcinoma; however, there is no evidence that *Fasciola* infections are associated with hepatobiliary tract cancer.<sup>12</sup> Hepatic imaging studies reveal multiple liver lesions in the acute hepatic phase of infection and various hepatobiliary tract abnormalities in the chronic phase.<sup>13</sup>

### Diagnostic Testing

Diagnosis by fecal examination for *Fasciola* eggs is problematic.<sup>1,14</sup> Eggs are not present in the stool during the acute phase of infection, and egg production is irregular in chronic infections (Figure 4). Egg morphology cannot reliably distinguish *F. hepatica* from *F. gigantica*. *Fasciola* spp. eggs can be difficult to distinguish from eggs of other trematodes, for example *Fasciolopsis buski* (the giant intestinal fluke). Recovering adult worms in endoscopic or surgical specimens is definitive and allows species identification based on the adult size of *F.*



Figure 3. Unstained Adult of *Fasciola Hepatica* Fixed in Formalin. Source: <https://www.cdc.gov/parasites/fasciola/epi.html>



Figure 4. *Fasciola Hepatica* Egg in An Unstained Wet Mount (400x Magnification). *Fasciola hepatica* eggs are broadly ellipsoidal, operculated, and measure 130–150 µm by 60–90 µm. Source: <https://www.cdc.gov/parasites/fasciola/diagnosis.html>

*hepatica* and *F. gigantica*. Serologic testing is beneficial for diagnosing both acute and chronic phase infections.<sup>1</sup> Specific antibodies to *Fasciola* become detectable 2 to 4 weeks after infection. Immunodiagnostic tests for fascioliasis include an enzyme immunoassay (EIA) with ES or recombinant antigens with confirmatory testing of EIA-positive specimens with an immunoblot assay.<sup>1,15</sup> Serological testing is available from commercial reference laboratories and the CDC. Current serological testing is reliable for both *F. hepatica* and *F. gigantica* infections but does not discriminate between the 2 species. Immunodiagnostic testing methods continue to evolve, and sensitivities and specificities can be 94%.<sup>16,17</sup> However, both infections have similar clinical features and responses to treatment.

## Treatment

Triclabendazole is the drug of choice for fascioliasis.<sup>1,18</sup> The drug is active against immature and adult parasites and is an effective treatment for acute and chronic infections. In February 2019, the FDA approved triclabendazole treatment for fascioliasis in patients at least 6 years of age. Triclabendazole is given orally, with food, to improve absorption. The current recommended dosage is 2 oral doses of 10 mg/kg given 12 hours apart. After treatment, ELISA-based testing results become negative in 91% of the cured cases after 1 year and become negative 6 months after retreatment in the remaining cases.<sup>18</sup> However, triclabendazole resistance has been documented, particularly in infected animals and some infected humans.<sup>19,20</sup> An alternative drug, nitazoxanide, is available in the United States and may be an effective therapy in some patients.<sup>21</sup> The adult dosage is 500 mg orally with meals twice a day for 7 days. However, nitazoxanide was ineffective in the case-patient presented here. Praziquantel is active against most trematodes but is not active against *Fasciola* parasites and should not be used for fascioliasis.

## Review of Human Fascioliasis Acquired in the United States

Few cases of domestically acquired human fascioliasis have been reported in the United States. In 2010, Fried found 54 human cases reported in the United States during approximately 120 years.<sup>5</sup> Twenty-six cases were infected while outside the United States. Two cases were in Puerto Rico, 21 cases were in Hawai'i; only 2 proven and 3 probable patients were in the continental United States. Norton reported the first case of human fascioliasis acquired in the United States in 1961.<sup>22</sup> In this report, Norton describes a 50-year-old woman in California who developed upper abdominal pain and tenderness. Laboratory test results were normal, and there was no eosinophilia. She underwent a cholecystectomy, and a single adult *F. hepatica* fluke was discovered incidentally in the common bile duct. Her symptoms resolved after the fluke was extracted.

Further history revealed that 10 years earlier, while living on a livestock ranch in California, she and 3 neighbors had gathered and eaten raw wild watercress. Some weeks later,

she developed right upper abdominal pain, erythema nodosum, and eosinophilia; her 3 neighbors had similar symptoms. This patient probably had unrecognized acute fascioliasis followed by chronic fascioliasis. Neff reported a Florida man who developed right upper abdominal pain, eosinophilia, and abnormal liver imaging studies.<sup>23</sup> At laparoscopy, serpiginous lesions were seen on the liver's surface; serological studies were positive for *F. hepatica*. The patient then admitted to having eaten wild watercress shortly before his illness. His symptoms resolved after treatment with triclabendazole. Perlada and Weisenberg reported 2 patients in northern California who developed acute hepatic fascioliasis after eating raw wild watercress, which they had shared.<sup>24</sup> Both patients had eosinophilia, liver lesions on imaging, and positive immunodiagnostic testing for fascioliasis. The patients recovered after triclabendazole treatment. One case report described a woman with a long history of liver and bowel disease diagnosed with fascioliasis after parasite fragments were recovered from a liver cyst and positive *Fasciola* serology tests.<sup>25</sup> Her infection was described as acquired in the United States; however, she had a history of traveling to France, where fascioliasis is more prevalent. In 1982, a limited survey of human fascioliasis in the US territory of Puerto Rico found 12 of 110 fecal samples positive for *F. hepatica* eggs; 11 of the 12 had a history of eating watercress grown on local farms.<sup>26</sup>

## Fascioliasis in Hawai'i

In 1938, Joseph E. Alicata, PhD, a noted parasitologist in Hawai'i, described the life history of *F. gigantica*, the common liver fluke of cattle in Hawai'i.<sup>27</sup> The parasite was first reported in Hawai'i cattle in 1892. The snail intermediate host was a freshwater snail, *Fossaria ollula*, found in wet lowlands where cattle fluke infections were common. *F. gigantica* infections were believed to have been introduced into Hawai'i by water buffalo from Asia, which spread *F. gigantica* infections to Hawai'i cattle, sheep, goats, and swine.<sup>28</sup> Alicata reviewed a 46-year history of human fascioliasis in Hawai'i.<sup>6</sup> At that time, cattle in the Hawaiian Islands were commonly infected with *F. gigantica*; only 1 infection was due to *F. hepatica*. Alicata's review included 19 cases of human *F. gigantica* infection in the Hawaiian Islands.<sup>6</sup> The first case was described in 1906, and in all cases, adult *F. gigantica* flukes were discovered by chance during surgical operations. Mature flukes were recovered from the liver and ectopic sites in the peritoneal cavity, upper respiratory tract, skin, and in 1 case, in the external ear canal. Stemmermann reviewed Alicata's cases and added 3 more cases, including 1 autopsy case.<sup>29</sup> He described cattle grazing in unfenced wetlands, which were also used for growing watercress for local markets. At the time, hog hunters reported finding liver flukes in wild hogs, known to frequent these wetlands. *F. gigantica* accounted for all the infections in which flukes were found. Many patients had been symptomatic for 3 months to 10 years before the diagnosis was made. All patients resided in Hawai'i, but their travel histories and countries of origin were not described.

Animal fascioliasis is not a reportable disease in Hawai'i or the United States, and current information regarding animal disease in Hawai'i is unavailable. Before 1995, the Hawai'i State Department of Agriculture was responsible for animal slaughterhouse food inspections. Animal liver fluke infections, detected by gross inspection of the liver, were described as widespread. In 1995, this responsibility was assumed by the US Department of Agriculture (personal communication from Jason Moniz, DVM; Hawai'i Animal Disease Control Branch). Animal fascioliasis is enzootic in regions of the continental United States, primarily in the Gulf coast regions with high annual rainfall, and in California and other western states with areas of poorly drained or irrigated pastures.<sup>30</sup>

Most human fascioliasis cases are due to eating raw watercress or other aquatic plants harvested from areas contaminated by infected livestock.<sup>7</sup> Nearly all human fascioliasis cases acquired in the United States are caused by eating raw wild watercress. In France, a 2002 outbreak of acute human fascioliasis was attributed to ingesting watercress grown in a commercial aquaculture bed adjacent to a cattle pasture.<sup>31</sup> The popular perception of the health benefits of watercress and the practice of foraging for wild foods may increase human fascioliasis infections in the United States.

## Conclusion

Few physicians in industrialized countries are familiar with fascioliasis. Most of the reported cases described above were unsuspected until an adult fluke was discovered incidentally during an investigation of hepatobiliary diseases. A patient history of eating raw, wild watercress is an important clue to the diagnosis, but this history was usually obtained after fascioliasis was diagnosed by other means. Likely, human fascioliasis occurs more often in the United States than is reported in the medical literature. Physicians should consider fascioliasis in travelers and immigrants from endemic areas who present with acute hepatitis with eosinophilia or chronic or intermittent hepatobiliary disease.<sup>32</sup> A history of eating raw wild watercress or other raw freshwater aquatic plants is an important diagnostic clue. The diagnosis is best made with immunodiagnostic testing performed at reference laboratories. Treatment with triclabendazole is usually curative. The case-patient with acute hepatic fascioliasis described here indicates that fascioliasis persists in Hawai'i livestock, and eating raw wild watercress is a risk for infection. However, the rarity of human infections in Hawai'i suggests that it is safe to eat commercially grown watercress cultivated in Hawai'i.

## Conflict of Interest

The author has no disclosures or conflicts of interest.

## Disclosure Statement

The use of the CDC investigational drug, triclabendazole, was approved under CDC Investigational New Drug Number 10.2877. This study was approved by The Queen's Medical Center's Research & Institutional Review Committee, and the patient consented to treatment.

## Acknowledgment

I want to thank the Research and Institutional Review Committee of The Queen's Medical Center in Honolulu, HI, and the CDC for their support and advice.

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